Ligands for the dopamine D2-like receptors

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Chapter 6

Derivatives of Nemonapride (YM-09151-2). Attempts to Develop a Selective Dopamine D_4 Antagonist

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Abstract

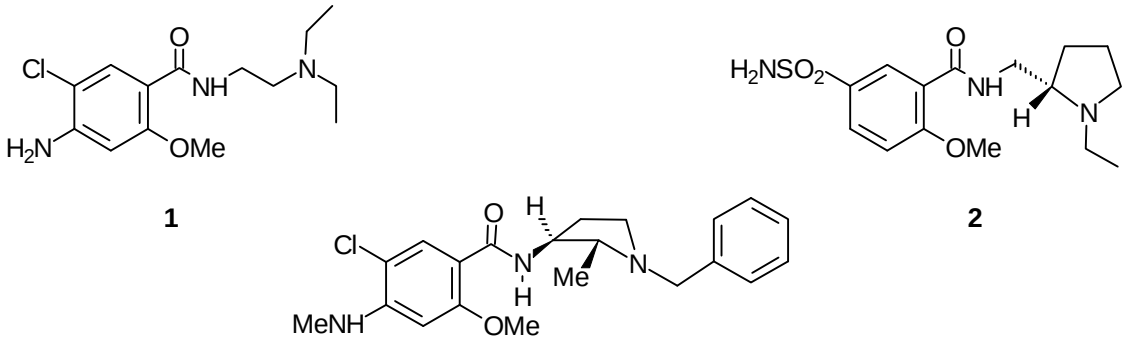
Nemonapride (**3**, YM-09151-2) is a well-known dopamine (DA) receptor antagonist, with high affinity for DA D_2, D_3 and D_4 receptors. By synthesizing derivatives (substituted *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides) that are different from nemonapride in the substitution pattern on the benzamide phenyl moiety, we have tried to eliminate affinity for the DA D_2 and D_3 receptors, in order to obtain a selective DA D_4 antagonist. The new compounds were evaluated in binding assays for human DA D_{2L}, D_3 and $D_{4.2}$ receptors. The structure affinity relationships that were found for the series of benzamides in Chapter 5, turned out to be applicable to this series of nemonapride derivatives only to a limited extent. Although some of the derivatives have high affinity for DA receptors, most of them are non-selective.

6.1 Introduction

In 1981 the Yamanouchi Pharmaceutical Company undertook a large SAR study with the aim to develop a highly potent dopamine antagonist of the benzamide type.[1] Starting from metoclopramide (**1**, Fig. 6.1) and sulpiride (**2**), benzamides that were known for their neuroleptic activity, nemonapride (**3**, YM-09151-2, formerly also known as emonapride) was developed. Nemonapride was the most potent dopamine antagonist from the series that was studied, displaying higher affinity for dopamine receptors in canine caudate nucleus than chlorpromazine and haloperidol (30 times and 3 times, respectively).[2] The compound is studied in its racemic form. Nemonapride has proven its value in numerous studies, both as a dopamine antagonist in

pharmacological studies, and as a dopamine receptor radioligand.[3-5] Initially, nemonapride was characterized as a potent neuroleptic, showing higher potency than haloperidol in inhibiting apomorphine induced stereotypy in rats,[1] but with a weaker cataleptogenic effect in the rat than the classic neuroleptics haloperidol and chlorpromazine.[6] Later, when cloned DA receptor subtypes became available, nemonapride was found to be a non-selective dopamine antagonist with sub-nanomolar affinity for DA D_2, D_3 and D_4 receptor subtypes.[7,8]

Nemonapride has a particular chloro-methoxy-methylamino substitution pattern on the benzamide aromatic ring, which is also found in drugs like metoclopramide (**1**). Furthermore, it has a pyrrolidine ring with a methyl group attached in a *cis*-orientation with respect to the benzamide attachment. The structure of the compound was studied with single crystal X-ray spectroscopy, which revealed an intramolecular hydrogen bond between the amide hydrogen and the methoxyl oxygen atom,[2] which is a common feature for *ortho*-methoxy benzamides. This hydrogen bond forms a virtual six-membered ring fused with the benzene ring, which has been speculated to function as a pseudo-aromatic ring forming the phenyl ring of the DA pharmacophore.[9,10]



1 **2** **3**

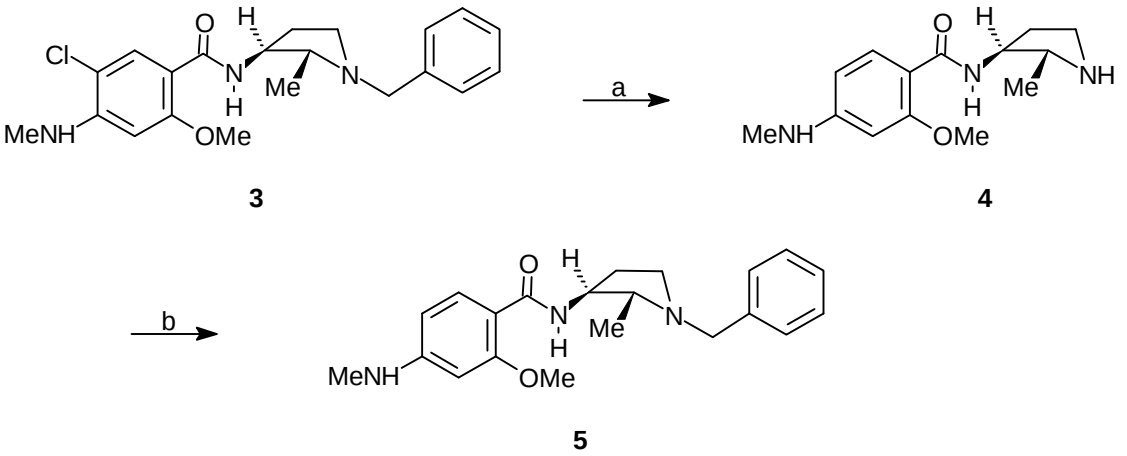
Figure 6.1 Chemical structures of metoclopramide (**1**), sulpiride (**2**), and nemonapride (**3**).

In the previously studied series of *N*-(1-benzyl-piperidin-4-yl)benzamides (Chapter 5) we found that the affinity for the DA D_2 receptor subtype of compounds without *ortho*-methoxy group, was decreased as compared to analogous benzamides with an *ortho*-methoxy group. The intramolecular hydrogen bond between amide -NH- and the *ortho*-methoxy group leads to a coplanar arrangement of the amide carbonyl with respect to the aromatic ring plane.[11] We concluded that this conformation is probably required for DA D_2 affinity, but does not appear to be essential for DA D_4 affinity. In order to develop an antagonist with high affinity and selectivity for the DA D_4 receptor subtype, we decided to apply this finding to nemonapride. By removing the *ortho*-methoxy group of this compound, we may be able to eliminate its affinity for the DA D_2 receptor subtype (and possibly also for the DA D_3 receptor subtype), thereby increasing its selectivity for the DA D_4 receptor. Therefore, we decided to synthesize the "des-methoxy" analogue of nemonapride, as well as several other analogues which are different from

nemonapride in their substitution pattern on the benzamide phenyl moiety. The new compounds were evaluated in binding assays for human DA D_2, D_3 and D_4 receptors.

6.2 Chemistry

"Des-chloro" nemonapride (**5**) was prepared by reducing nemonapride (**3**) catalytically with palladium on carbon, employing ammonium formate as a hydrogen donor, which gave **4** as the product (Scheme 6.1). However, this reduction not only removed the aromatic chlorine but also the benzyl group. Therefore, **4** was re-benzylated in a simple alkylation reaction with benzyl chloride, using cesium carbonate as a base.

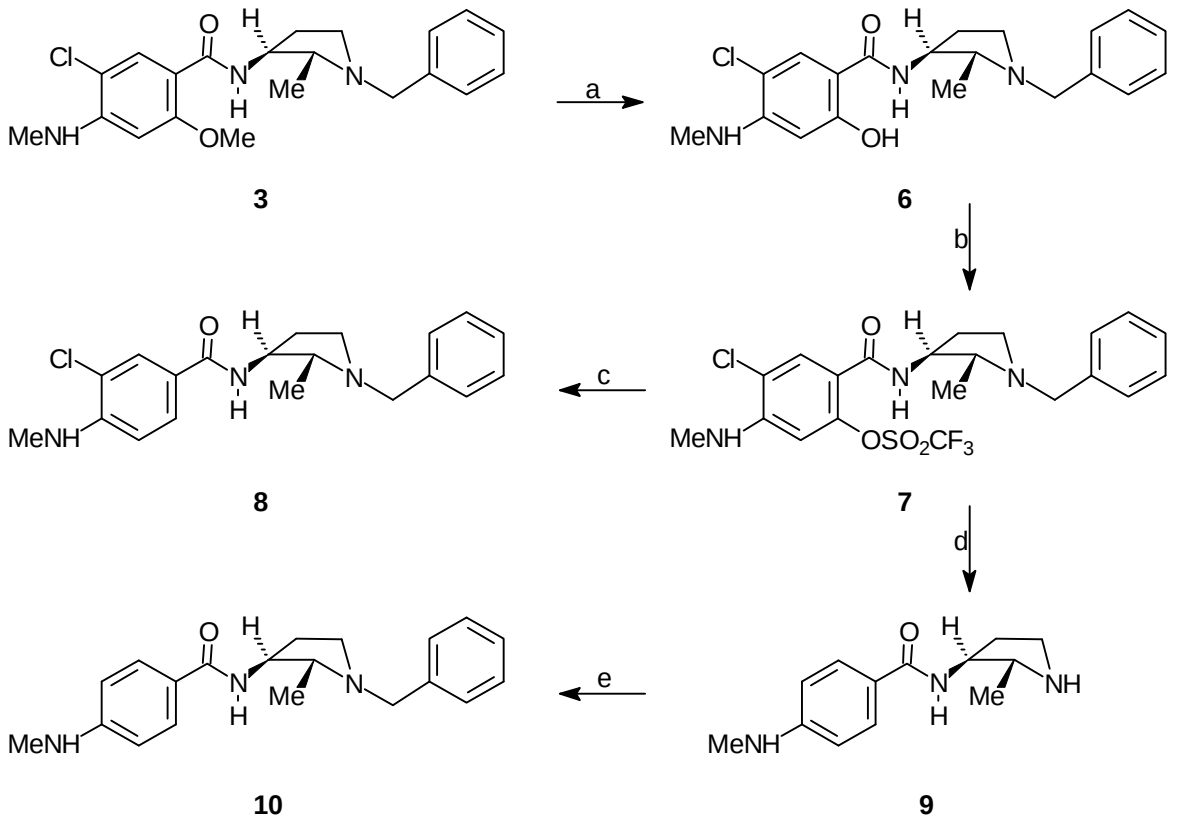


3 **4** **5**

Scheme 6.1 (a) HCO_2NH_4, 10% Pd/C, MeOH; (b) $PhCH_2Cl$, Cs_2CO_3, MeCN.

The "des-methoxy" derivative of nemonapride (**8**) was prepared as follows (Scheme 6.2). Nemonapride (**3**) was demethylated with boron tribromide to yield the corresponding hydroxy derivative (**6**).[12] Compound **6** was subsequently triflated with *N*-phenyltrifluoromethanesulfonimide to give **7**, which was subjected to a selective catalytic reduction to remove the triflate group without affecting the aromatic chlorine or the benzyl group, to yield derivative **8**.[13]

Triflate **7** was also subjected to a non-selective catalytic reduction with palladium on carbon and ammonium formate (Scheme 6.2), which eliminated both the aromatic chlorine and the triflate group. Intermerdiate **9** was then re-benzylated to yield derivative **10**.



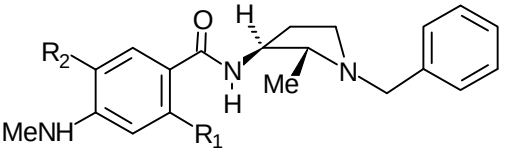
3 **6** **8** **7** **9** **10**

Scheme 6.2 (a) BBr_3, HCl/Et_2O, CH_2Cl_2, 0 °C; (b) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2; (c) Et_3N, HCO_2H, PPh_3, $Pd(OAc)_2$, 60 °C; (d) HCO_2NH_4, 10% Pd/C, MeOH; (e) $PhCH_2Cl$, Cs_2CO_3, MeCN.

6.3 Receptor Binding Studies

The *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides were tested for their *in vitro* binding affinity for cloned human dopamine (DA) D_{2L}, D_3 or $D_{4.2}$ receptors,[14] expressed in Chinese hamster ovary (CHO) K-1 cells. The affinities of the compounds were determined by their abilities to displace [^{3}H]-spiperone from human D_{2L}, D_3 or $D_{4.2}$ DA receptors. Receptor affinities are presented in Table 6.1. Nemonapride is included as a reference.

Table 6.1. DA receptor affinities of the *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides.



compound	R_1	R_2	competition for [^{3}H]-spiperone binding K_i, nM[a]		
			hD_{2L}	hD_3	$hD_{4.2}$
5	OMe	H	0.22	0.40	0.56
6	OH	Cl	33	20	45
7	OSO_2CF_3	Cl	1370	570	350
8	H	Cl	22	8.4	31
10	H	H	200	60	59
3 (nemonapride)	OMe	Cl	0.09	0.30	0.15

[a] K_i values were obtained from six concentrations of each drug, run in triplicate, by a non-linear regression analysis, which varied less than 30 %.

6.4 Discussion

In this study we have tried to apply the structure affinity relationships that were found for the series of benzamides in Chapter 5, to nemonapride, to increase its selectivity for the DA D_4 receptor subtype. However, as can be seen from the receptor binding data in Table 6.1, none of the derivatives that were synthesized has a reasonable selectivity for the DA D_4 receptor. Nevertheless, some interesting structure-affinity relationships can be observed from Table 6.1.

Elimination of the aromatic chlorine on the 5-position reduces the affinity for DA receptors slightly, resulting in the non-selective derivative **5** with high affinity for all three receptor subtypes. Manipulation of the other substituents has a more dramatic effect on the receptor binding profile. For example, when also the *ortho*-methoxy group is taken away (compound **10**) the affinity for the DA D_2 receptor is reduced by about a factor 1000, whereas affinity for the DA D_4 receptor subtype is reduced by a factor 100, as compared to **5**. This effect is comparable to the structure-affinity relationships found for the benzamides in Chapter 5, for which elimination of the *ortho*-methoxy group resulted in a larger reduction in affinity for the DA D_2 than for the DA D_4 receptor subtype. Thus, also for this series of *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)benzamides the *ortho*-methoxy group appears to be more important for DA D_2 binding than for DA D_4 binding.

The affinity of hydroxy derivative **6** is reduced by about a factor 100 for all three DA receptor subtypes, as compared to nemonapride. This *ortho*-hydroxy group may form an intramolecular hydrogen bond with the amide carbonyl oxygen,[15] thereby rotating the entire

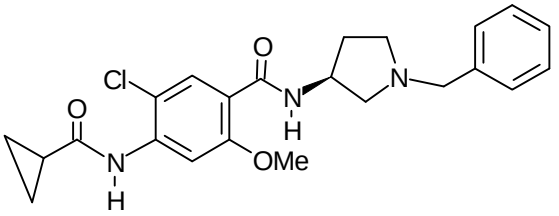
amide phenyl moiety by 180 ° (see section 5.4). It is easy to imagine that such a conformational change has a dramatic effect on the DA receptor binding profile.

The triflated compound **7** has a much reduced affinity for these DA receptors. Although the trifluoromethanesulfonyloxy group serves as a valuable bio-isoster of a methoxy and/or hydroxy group within other drug classes,[16,17] the binding data show that this approach is not suitable for this series of nemonapride derivatives. The low affinity of **7** may be explained electronically, because of the strong electron withdrawing properties of the triflate substituent, but also sterically, because the size of this substituent may distort the coplanar arrangement of amide carbonyl and phenyl ring.

Compound **8**, which has no methoxy group as compared to nemonapride, does not have the desired DA D_4 selectivity which we had expected on the basis of the structure affinity relationships found in Chapter 5. When compared to compound **10** the aromatic chlorine atom of **8** seems to eliminate the DA D_4 preferring properties of the des-methoxy derivatives.

In conclusion, eliminating the *ortho*-methoxy group to enhance DA D_4 selectivity within this series is only effective when no aromatic chlorine substituent is present on the 5 position. Compound **10** has some selectivity for the DA D_4 receptor (over the DA D_2 receptor), but its affinity as compared to nemonapride has been reduced dramatically.

Recently, the Yamanouchi Pharmaceutical Company developed a selective DA D_4 antagonist from a series of *N*-(1-benzylpyrrolidin-3-yl)benzamides, related to nemonapride.[18,19] *(S)*-(+)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenz-amide (YM-43611, **11**), showed high affinity for DA D_3 and D_4 receptors (K_i values of 21 and 2.1 nM, respectively) with 110-fold DA D_4 selectivity over DA D_2 receptors. Apparently, for this series of compounds selectivity for the DA D_4 receptor is more effectively obtained by manipulating other structural features.



11 (YM-43611)

6.5 Experimental Section

General. Physical and spectral data were obtained as described in section 5.5. In addition, 500 MHz spectra were obtained on a Varian Unity 500 spectrometer. MPLC and recrystallization procedures were also performed as described in Section 5.5.

Materials. Nemonapride was kindly provided by Parke Davis Pharmaceutical Research. Acetonitril was dried on molecular sieves 4Å. All other chemicals and solvents are commercially available, and were used without further purification.

Nemonapride (3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.4, 3H), 1.56-1.68 (m, 1H), 2.05-2.30 (m, 2H), 2.56-2.68 (m, 1H), 2.95 (d, *J* = 5.1, 3H), 2.92-3.02 (m, 1H), 3.17 (d, *J* = 13.2, 1H), 3.98 (s, 3H), 4.04 (d, *J* = 13.2, 1H), 4.59-4.75 (m, 2H), 6.12 (s, 1H), 7.22-7.38 (m, 5H), 8.01 (d, *J* = 12.0, 1H), 8.10 (s, 1H); ^{13}C NMR δ 13.8, 29.9, 30.9, 51.5, 52.1, 55.9, 57.4, 61.5, 93.0, 110.5, 111.2, 126.7, 128.0 (2C), 128.5 (2C), 132.2, 147.9, 158.0, 164.0, 169.0.

***cis*-*N*-(2-Methylpyrrolidin-3-yl)-2-methoxy-4-(methylamino)-benzamide (4).** Nemonapride **3** (0.17 g, 0.43 mmol) and ammonium formate (0.12 g, 1.9 mmol) were dissolved in 10 mL of methanol, and the solution was treated (under N_2) with 10% Pd/C (0.15 g). The reaction mixture was stirred at room temperature, while monitoring the reaction with TLC. After 40 min all starting material was consumed, and the Pd/C was removed by filtration over Celite, after which the solvent was evaporated under reduced pressure. Because the residue contained some ammonium formate, it was resuspended in acetonitril. The solids were filtered off, and the acetonitril was evaporated under reduced pressure which yielded **4** as a clear oil (0.11 g, 97 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.6, 3H), 2.12-2.18 (m, 1H), 2.44-2.51 (m, 1H), 2.82 (s, 3H), 3.19-3.26 (m, 1H), 3.50-3.58 (m, 1H), 3.68 (s, 1H), 3.72-3.78 (m, 1H), 3.89-4.01 (m, 4H), 4.62-4.70 (m, 1H), 6.05 (s, 1H), 6.21 (d, *J* = 8.7, 1H), 7.85 (d, *J* = 8.7, 1H), 8.20 (d, *J* = 8.1, 1H); ^{13}C NMR δ 12.4, 30.0, 30.9, 43.4, 51.0, 55.8, 58.2, 63.7, 94.0, 104.7, 133.3, 153.9, 159.6, 166.5. HRMS calcd. (obsd.) for $C_{14}H_{21}N_3O_2$ 263.1634 (263.1651).

***cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-2-methoxy-4-(methylamino)-benzamide (5).** Compound **4** (0.11 g, 0.43 mmol) and benzyl chloride (60 µL, 0.50 mmol) were dissolved in 5 mL of acetonitril. Cesium carbonate (0.27 g, 0.81 mmol) was added, and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residuals were fractionated between ethyl acetate and water, and the water layer was extracted once with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The residual oil was purified with MPLC on silica (initial eluent 100 % hexane, final eluent 100 % ethyl acetate), which yielded **5** as a clear oil (0.10 g, 66 %): MS (CI with NH_3) *m/e* 354 (M^{+1}). Part of the product was converted to the oxalate and recrystallized from 2-propanol, which yielded white crystals: mp 172-175 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.4, 3H), 1.58-1.72 (m, 1H), 2.10-2.30 (m, 2H), 2.57-2.68 (m, 1H), 2.87 (d, *J* = 3.4, 3H), 2.92-3.01 (m, 1H), 3.17 (d, *J* = 13.0, 1H), 3.94 (s, 3H), 4.04 (d, *J* = 13.0, 1H), 4.10-4.24 (m, 1H), 4.60-4.74 (m, 1H), 6.09 (d, *J* = 2.0, 1H), 6.27 (dd, J_1 = 8.6, J_2 = 2.2, 1H), 7.24-7.38 (m, 5H), 8.04 (d, *J* = 8.8, 2H); ^{13}C NMR δ 13.9, 30.1, 31.0, 51.5, 51.9, 55.4, 57.4, 61.5, 94.2, 104.8, 110.5, 126.7, 128.0 (2C), 128.5 (2C), 133.6, 139.5, 153.0, 159.2, 165.1. Anal. calcd. (obsd.) for $C_{21}H_{27}N_3O_2 \cdot C_2H_2O_4 \cdot {}^1/_3H_2O$: C: 61.40 (61.65), H: 6.60 (6.70), N: 9.34 (8.88).

***cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-hydroxy-4-(methylamino)-benzamide (6).** A solution of nemonapride **3** (0.26 g, 0.68 mmol) in 5 mL of methylene chloride was treated with 1 N HCl-ether (1.35 mL, 1.35 mmol). The mixture was cooled on ice, and BBr_3 (0.68 mL of a 1 N solution in methylene chloride, diluted with 1 mL of methylene chloride, 0.68 mmol) was added dropwise, over a 1 h period. After the addition was completed, the reaction was stirred at 0 °C for 1 h. The mixture was basified with 5 % ammonia, and the layers were separated. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, which yielded **6** as a white solid (0.26 g, 100 %). Part of the product was converted to the hydrochloride and recrystallized from ethanol/isopropylether, which yielded white crystals: mp 221-223 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.4, 3H), 1.57-1.63 (m, 1H), 2.05-2.28 (m, 2H), 2.53-2.59 (m, 1H), 2.91 (d, *J* = 4.9, 3H), 2.94-3.01 (m, 1H), 3.13 (d, *J* = 12.8, 1H), 4.05 (d, *J* = 12.8, 1H), 4.62-4.72 (m, 2H), 6.16 (s, 1H), 6.41 (br d, *J* = 9.3, 1H), 7.26-7.35 (m, 7H); ^{13}C NMR δ 13.3, 29.8, 30.3, 51.3, 51.6, 57.3, 62.1, 98.0, 103.2, 109.2, 125.4, 127.0, 128.2 (2C), 128.9 (2C), 138.2, 149.2, 162.6, 168.7; MS (CI with NH_3) *m/e* 374 (M^{+1}). Anal. calcd. (obsd.) for $C_{20}H_{24}ClN_3O_2 \cdot HCl$: C: 58.54 (58.23), H: 6.14 (6.04), N: 10.24 (10.18).

***cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-4-(methylamino)-2-[[(trifluoro-methyl)-sulfonyl]oxy]benzamide (7).** Compound **6** (0.26 g, 0.68 mmol) was dissolved in methylene chloride (10 mL), and triethylamine (0.6 mL, 4.3 mmol) and *N*-phenyltrifluoromethanesulfonimide (0.78 g, 2.2 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, after which extra triethylamine (0.6 mL, 4.3 mmol) and *N*-phenyltrifluoromethanesulfonimide (0.3 g, 0.85 mmol) were added. When all starting compound was consumed (TLC), the reaction mixture was washed with water (20 mL). The aqueous layer was extracted once with methylene chloride (20 mL), after which the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil contained a substantial amount of *N*-phenyltrifluoromethanesulfonamide, and the product was purified by MPLC on silica (initial eluent 100% hexane, final eluent 100% ethyl acetate) which yielded **7** as a clear oil (0.31 g, 90 %). Part of the product was converted to the oxalate and recrystallized from ethyl acetate/hexane yielding light-yellow crystals: mp 165.5-166.5 °C. ^{1}H NMR (500 MHz, CD_3OD, oxalate) δ 1.35 (d, *J* = 6.6, 3H), 2.09-2.17 (m, 1H), 2.49-2.56 (m, 1H), 2.88 (s, 3H), 3.19-3.25 (m, 1H), 3.31-3.32 (m, 1H), 3.51-3.57 (m, 1H), 3.80-3.84 (m, 1H), 4.25 (d, *J* = 12.9, 1H), 4.59 (d, *J* = 12.9, 1H), 4.68-4.73 (m, 1H), 6.48 (s, 1H), 7.46-7.48 (m, 3H), 7.55-7.57 (m, 2H), 7.69 (s, 1H); ^{13}C NMR (125.7 MHz, CD_3OD, oxalate) δ 11.6, 28.8, 30.0, 49.3, 52.9, 57.6, 66.5, 104.0, 115.6, 118.4, 120.1 (q, *J* = 321 Hz, CF_3), 130.4 (2C), 131.0, 131.1, 131.5, 131.7 (2C), 148.9, 150.3, 166.6 (2C), 167.2; MS (CI with NH_3) *m/e* 506 (M^{+1}). Anal. calcd. (obsd.) for $C_{21}H_{23}ClF_3N_3O_4S \cdot C_2H_2O_4$: C: 46.35 (46.09), H: 4.23 (4.02), N: 7.05 (7.06).

***cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-3-chloro-4-(methylamino)-benzamide (8).** Triflate **7** (0.11 g, 0.22 mmol) was dissolved in 3 mL of DMF, and triethylamine (120 μL, 0.87 mmol), formic acid (33 μL, 0.87 mmol), triphenylphosphine (12 mg, 0.043 mmol) and palladium acetate (7.3 mg, 0.033 mmol) were added. The reaction mixture was heated to 60 °C under a nitrogen atmosphere for 5 h. After cooling to room temperature, 5 % hydrochloric acid (3 mL) was added, and the mixture was stirred overnight. The mixture was basified with 10 % sodium hydroxide until pH = 10, and extracted with methylene chloride (3 × 10 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual oil was purified with MPLC on silica (initial eluent 99 % hexane + 1 % triethyl amine, final eluent 99 % ethyl acetate + 1 % triethyl amine) which yielded **8** as a clear oil (0.073 g, 93 %): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.3, 3H), 1.55-1.68 (m, 1H), 2.02-2.31 (m, 2H), 2.53-2.62 (m, 1H), 2.86-3.00 (m, 4H), 3.12 (d, *J* = 12.8, 1H), 4.03 (d, *J* = 12.8, 1H), 4.62-4.73 (m, 2H), 6.46 (d, *J* = 9.5, 1H), 6.60 (d, *J* = 8.6, 1H), 7.22-7.51 (m, 7H), 7.63 (dd, J_1 = 8.6, J_2 = 2.2, 1H), 7.77 (d, *J* = 2.2, 1H); ^{13}C NMR δ 13.4, 29.9, 30.5, 51.5, 51.9, 57.5, 62.3, 109.3, 118.4, 122.7, 126.8, 127.0, 128.2 (2C), 128.9 (2C), 131.9, 138.3, 147.2, 165.7; MS (CI with NH_3) *m/e* 358 (M^{+1}). The product was converted to the oxalate but failed to crystallize, and was obtained as an off-white foam. Anal. calcd. (obsd.) for $C_{20}H_{24}ClN_3O \cdot C_2H_2O_4 \cdot ¾H_2O$: C: 57.21 (57.49), H: 5.96 (5.73), N: 9.10 (8.71).

***cis*-*N*-(2-Methylpyrrolidin-3-yl)-4-(methylamino)-benzamide (9).** Triflate **7** (0.14 g, 0.28 mmol) was converted to **9**, as described for the preparation of **4**, and was isolated as a clear oil (0.05 g, 80 %). The intermediate was used without further purification.

***cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-4-(methylamino)-benzamide (10).** Compound **9** (0.05 g, 0.23 mmol) was benzylated as described for the preparation of **5**, which afforded **10** as a light-brown oil (0.027 g, 36 %): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.1, 3H), 1.60-1.67 (m, 1H), 2.02-2.29 (m, 2H), 2.59-2.65 (m, 1H), 2.92-3.07 (m, 1H), 3.09 (s, 3H), 3.18 (d, *J* = 11.5, 1H), 4.07 (d, *J* = 11.5, 1H), 4.60 (s, 1H), 4.69-4.76 (m, 1H), 6.71 (d, *J* = 8.8, 2H), 7.15-7.38 (m, 6H), 7.71 (d, *J* = 9.0, 2H); MS (CI with NH_3) *m/e* 324 (M^{+1}).

Pharmacology. Receptor Binding Assays. The receptor binding studies were performed at Parke Davis Pharmaceutical Research Division, by T.A. Pugsley, as described in section 5.5.

Acknowledgement. Y.-H. Shih, K. Zoski, L. Georgic and H. Akunne are gratefully acknowledged for the *in vitro* pharmacology testing.

6.6 References

(1) Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. Synthesis and neuroleptic activity of benzamides. Cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide and related compounds. *J. Med. Chem.* **1981**, *24*, 1224-1230.

(2) Furuya, T.; Iwanami, S.; Takenaka, A.; Sasada, Y. New Potent Neuroleptic Drugs of Benzamide Derivatives. I. Crystal and Molecular Structure of *N*-[(2*RS*, 3*RS*)-1-Benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 2321-2326.

(3) Hatano, K.; Ishiwata, K.; Kawashima, K.; Hatazawa, J.; Itoh, M.; Ido, T. D2-dopamine receptor specific brain uptake of carbon-11-labeled YM-09151-2. *J. Nucl. Med.* **1989**, *30*, 515-522.

(4) Niznik, H. B.; Grigoriadis, D. E.; Pri Bar, I.; Buchman, O.; Seeman, P. Dopamine D2 receptors selectively labeled by a benzamide neuroleptic: [3H]-YM-09151-2. *Naunyn Schmiedebergs Arch. Pharmacol.* **1985**, *329*, 333-343.

(5) Seeman, P.; Guan, H. C.; Van Tol, H. H. Schizophrenia: elevation of dopamine D4-like sites, using [3H]nemonapride and [125I]epidepride. *Eur. J. Pharmacol.* **1995**, *286*, R3-5.

(6) Yamamoto, M.; Usuda, S.; Tachikawa, S.; Maeno, H. Pharmacological studies on a new benzamide derivative, YM-09151-2, with potential neuroleptic properties. *Neuropharmacology* **1982**, *21*, 945-951.

(7) Seeman, P.; Guan, H. C.; Van Tol, H. H. Dopamine D4 receptors elevated in schizophrenia [see comments]. *Nature* **1993**, *365*, 441-445.

(8) Tang, L.; Todd, R. D.; Heller, A.; O'Malley, K. L. Pharmacological and functional characterization of D2, D3 and D4 dopamine receptors in fibroblast and dopaminergic cell lines [published erratum appears in J Pharmacol Exp Ther 1994 Sep; 270(3):1397]. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 495-502.

(9) Van de Waterbeemd, H.; Testa, B. Theoretical Conformational Studies of Some Dopamine Antagonistic Benzamide Drugs: 3-Pyrrolidyl- and 4-Piperidyl Derivatives. *J. Med. Chem.* **1983**, *26*, 203-207.

(10) Testa, B.; Van de Waterbeemd, H.; Carrupt, P. A. Conformation, Electrostatic Potential and Pharmacophoric Pattern of Orthopramides and Other Dopamine Receptor Antagonists. *J. Mol. Struct. (Theochem)* **1986**, *134*, 351-366.

(11) Högberg, T. The development of dopamine D2-receptor selective antagonists. *Drug Des. Discov.* **1993**, *9*, 333-350.

(12) de Paulis, T.; Kumar, Y.; Johansson, L.; Rämsby, S.; Florvall, L.; Hall, H.; Ängeby Möller, K.; Ögren, S. O. Potential neuroleptic agents. 3. Chemistry and antidopaminergic properties of substituted 6-methoxysalicylamides. *J. Med. Chem.* **1985**, *28*, 1263-1269.

(13) Sonesson, C.; Lin, C. H.; Hansson, L.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Wikström, H. Substituted (S)-phenylpiperidines and rigid congeners as preferential dopamine autoreceptor antagonists: synthesis and structure-activity relationships. *J. Med. Chem.* **1994**, *37*, 2735-2753.

(14) Shih, Y. H.; Akunne, H. C.; Zoski, K. T.; Georgic, L. M.; Pugsley, T. A. Interactions of BMY 14802 with Subtypes of Dopamine Receptors. *Pharmacological Communications* **1996**, *7*, 243-250.

(15) Högberg, T. Novel Substituted Salicylamides and Benzamides as Selective Dopamine D_2-receptor Antagonists. *Drugs Fut.* **1991**, *16*, 333-357.

(16) Sonesson, C.; Barf, T.; Nilsson, J.; Dijkstra, D.; Carlsson, A.; Svensson, K.; Smith, M. W.; Martin, I. J.; Duncan, J. N.; King, L. J.; Wikström, H. Synthesis and evaluation of pharmacological and pharmacokinetic properties of monopropyl analogs of 5-, 7-, and 8-[[(trifluoromethyl)sulfonyl]oxy]-2-aminotetralins: central dopamine and serotonin receptor activity. *J. Med. Chem.* **1995**, *38*, 1319-1329.

(17) Sonesson, C.; Boije, M.; Svensson, K.; Ekman, A.; Carlsson, A.; Romero, A. G.; Martin, I. J.; Duncan, J. N.; King, L. J.; Wikström, H. Orally active central dopamine and serotonin receptor ligands: 5-, 6-, 7-, and 8-[[trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralins and the formation of active metabolites in vivo. *J. Med. Chem.* **1993**, *36*, 3409-3416.

(18) Ohmori, J.; Maeno, K.; Hidaka, K.; Nakato, K.; Matsumoto, M.; Tada, S.; Hattori, H.; Sakamoto, S.; Tsukamoto, S.; Usuda, S.; Mase, T. Dopamine D3 and D4 receptor antagonists: synthesis and structure--activity relationships of (S)-(+)-N-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4- [(cyclopropylcarbonyl) amino]-2-methoxybenzamide (YM-43611) and related compounds. *J. Med. Chem.* **1996**, *39*, 2764-2772.

(19) Hidaka, K.; Tada, S.; Matsumoto, M.; Ohmori, J.; Tasaki, Y.; Nomura, T.; Usuda, S.; Yamaguchi, T. In vitro pharmacological profile of YM-43611, a novel D2-like receptor antagonist with high affinity and selectivity for dopamine D3 and D4 receptors. *Br. J. Pharmacol.* **1996**, *117*, 1625-1632.